REMARKS

Claims 1-8, 11 and 13-19 are pending in the application. In the instant amendment, claim 11 has been amended to clarify the present invention. Claim 67 has been added to the present application. Upon entry of the above-made amendments, claims 1-8, 11 13-19 and 67 will be pending. Claim 11 has been amended to delete recitation of "and SEQ ID NO:10." Support for amended claim 11 is found in the specification at page 36, lines 20-23; page 9, lines 17-18, 25-27; page 12, lines 31-36. Support for new claim 67 is found in the specification at page 24, lines 6-14; page 50, lines 19-24 and 31-36.

No new matter has been added by these amendments. Entry of the foregoing amendments is respectfully requested.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-5, 7, 8, 11, 13, 15, 16 and 19 under 35 U.S.C. § 102(b) as anticipated by International Publication No. WO 96/22384 by Lemke and Hansen ("Lemke"). The Examiner alleges that this reference "teaches various anti-CD30 antibodies in [the] treatment of Hodgkin's disease throughout the entire article," referring specifically to pages 8-11 and to claims 13 and 14 (Office Action at page 2). With respect to claim 11, the Examiner further alleges that various antibodies taught by Lemke inherently have an antibody light chain having at least 95% identity to SEQ ID NO:2 of the instant application (Office Action at page 2). Respectfully, Applicants disagree, and submit that Lemke does not anticipate the claims.

A reference must be cited for what it fairly teaches. *In re Burkel*, 201 U.S.P.Q. 67 (C.C.P.A. 1979). Lemke teaches and discloses anti-CD30 antibodies that do not promote the release of CD30 from a cell surface, but instead inhibit the release of soluble CD30, and are specific for Hodgkin and Sternberg-Reed cells, making those antibodies potentially useful in the delivery of toxins to Hodgkin's disease cells (page 2, ¶ 3). Lemke suggests that the efficacy of antibody-toxin conjugates may be affected by the release of soluble CD30 ("sCD30"), because immunoconjugates can bind to both CD30 and sCD30. (Page 1, ¶¶ 3-4, discussing antibody Ki-1, the first CD30-binding antibody identified). In discussing the lack of efficacy of an immunoconjugate of antibody Ki-1 and ricin, Lemke notes that one cause could be the enhancement of release of sCD30 by Ki-1 (page 2, ¶ 1). Lemke notes that another antibody, Ber-H2, strongly inhibits the release of sCD30, but is not specific for

Hodgkin's disease cells (page 2, ¶ 2). Lemke's teaching of an antibody that reduces the amount of sCD30 released is embodied in claim 1 of Lemke, which specifically recites "[a]n antibody which binds to the CD30 antigen and a) releases sCD30 from Hodgkin's disease cell to an amount of, or less than, 10%, referred to [*i.e.*, as compared to] the release found without an addition of antibody . . ." Thus, the antibodies that Lemke teaches, as immunoconjugates for therapy of Hodgkin's disease are antibodies that inhibit the formation of sCD30 and are exemplified by Ki-4.

Lemke also differentiates anti-CD30 antibodies based on cross-binding experiments (*see* page 18; page 21, Table II). Lemke specifically identifies antibody Ki-4 as a preferred antibody of the invention (page 6, ¶ 5). Ki-4 is an antibody that significantly inhibits the release of CD30 from Hodgkin's tumor cells (page 18, ¶ 3). Lemke groups antibodies Ki-4 and Ber-H2 together in what it terms Cluster A. Two other antibodies, C10 (*i.e.*, AC10) and HeFi-1, are in a separate group, Cluster C (page 21, Table II). Lemke teaches that antibody HeFi-1 *enhances* the release of sCD30, while antibodies Ki-4 and Ber-H2 *inhibit* the release of sCD30(page 18, ¶ 2). Thus, Lemke teaches that antibodies that are specific for CD30, and which do not promote release of sCD30 (*e.g.*, those of Cluster A), are useful as immunoconjugates for the treatment of Hodgkin's disease, while antibodies that enhance release of sCD30 (*e.g.*, those of Cluster C) are taught to be ineffective.

Evidence shows that antibodies in what Lemke terms Cluster A do not have intrinsic cytotoxic or cytostatic effects. Engert *et al.*, "Evaluation of Ricin A Chain-containing Immunotoxins Directed Against the CD30 Antigen as Potential Reagents for the Treatment of Hodgkin's Disease," *Cancer Res.* 50:84-88 (1990) ("Engert"[1]) discloses that Ber-H2, when not conjugated to a toxin, failed to show any cytotoxicity towards Hodgkin's cell line L540 (page 86, right column, ¶ 2: "The cytotoxic effect of all of the immunotoxins was specific since the native antibodies . . . were not toxic at 10^{-6} M.").

In contrast, rejected claims 1-5 and 7 of the instant application require that the recited antibodies exert a cytotoxic or cytostatic effect on a Hodgkin's disease cell line in the absence of cells other than cells of the Hodgkin's disease cell line (*e.g.*, effector cells) or conjugation to a cytotoxic or cytostatic agent. As explained above, the antibodies taught for

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[1] Cited by Applicants in the Information Disclosure Statement filed June 4, 2001 as reference AJ.

therapeutic use by Lemke are not intrinsically cytotoxic or cytostatic. For at least these reasons, Lemke does not anticipate claims 1-5 or 7 under 35 U.S.C. § 102(b)

Lemke also does not anticipate claim 8, which requires that the recited protein compete with HeFi-1 or AC10 for binding to CD30. Lemke, as noted above, teaches that antibodies in Cluster A are useful for the treatment of Hodgkin's disease, and that Cluster A antibodies, such as Ki-4, do not compete with Cluster C antibodies, such as HeFi-1 or AC10, for binding to CD30. Lemke teaches that Ki-4, a member of Cluster A, fails to compete with HeFi-1 in Group C. (*See* Table II, page 21). Lemke therefore fails to teach for therapeutic use antibodies that compete with HeFi-1 or AC10 for binding to CD30, and does not anticipate claim 8.

Lemke also does not inherently anticipate claim 11. The Examiner contends that the antibodies taught by Lemke inherently have antibody light chains having at least 95% identity to SEQ ID NO: 2 [*sic*, SEQ ID NO:10], as evidenced by Weigert *et al.*, *Nature* 276:785,90 (1979).[2] (Applicants note that the sequence comparison to which the Examiner refers used SEQ ID NO: 10 and not SEQ ID NO: 2; Applicants proceed on the assumption that the Examiner meant to refer to SEQ ID NO: 10.) Applicants have amended claim 11 to delete recitation of SEQ ID NO: 10, thus mooting the rejection of this claim. Furthermore, claim 11 specifies the use of an AC10-related protein (since SEQ ID NO: 2 is the heavy chain variable region sequence of AC10), and is therefore also not anticipated since, as discussed above, AC10, being a member of Cluster C, is not suggested for therapeutic use by Lemke.

Because Lemke fails to anticipate claims 8 or 11, the reference also cannot anticipate any claims depending therefrom, *i.e.*, claims 13, 15, 16 and 19.

Lemke fails to anticipate any of claims 1-5, 7, 8, 11, 13, 15, 16 and 19 under 35 U.S.C. § 102(b). Therefore, Applicants respectfully request the Examiner withdraw the rejection of these claims on this basis.

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[2] The Examiner provided this reference in abstract form only. Applicants are making the full-length article of record in a Third Supplemental Information Disclosure, which is filed concurrently herewith.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103

The Examiner has rejected claims 6, 14, 17 and 18 over Lemke, as applied to claims 1-5, 7, 8, 11, 13, 15, 16 and 19, further in view of Barth *et al.*, "Ki-4(scFv)-ETA', a New Recombinant Anti-CD30 Immunoglobulin with Highly Specific Cytotoxic Activity Against Disseminated Hodgkin Tumors in SCID Mice," *Blood* 95(12):3909-14 (June 2000) ("Barth"). Claims 6, 15, 17 and 18 specify that the method of treating an individual using the recited anti-CD30 antibodies additionally comprises chemotherapy. The Examiner states that the claims are interpreted as drawn to a method of Hodgkin's disease treatment by administering an anti-CD30 antibody or a conjugated anti-CD30 antibody in combination with chemotherapy. The Examiner states that Barth teaches that conventional chemotherapy is effective against Hodgkin's disease and that anti-CD30 antibodies would be useful to kill residual tumor cells that could cause a relapse (Office Action at page 3). Applicants respectfully disagree that the two references render these claims obvious, as explained below.

As explained above, Lemke teaches that antibodies that specifically bind CD30 and inhibit the release of sCD30, such as antibody Ki-4, are useful in the treatment of Hodgkin's disease, but does not teach or suggest for therapeutic use against Hodgkin's disease the proteins and antibodies recited in the instant claims, which have functional activities that distinguish them from the antibodies suggested for use by Lemke. Barth teaches an immunotoxin consisting of an antibody Ki-4 single chain fragment fused to a deletion mutant of endotoxin A.

Claim 6, which depends from claim 1, requires that the recited antibody exert a cytostatic or cytotoxic effect on a Hodgkin's disease cell line in the absence of a cytotoxin or effector cell. As discussed above, Lemke fails to teach the use of an antibody or a protein that, by itself, exerts cytostatic or cytotoxic activity on a Hodgkin's disease cell line. This missing teaching is not supplied by Barth, which teaches activity against Hodgkin's lymphoma of an immunotoxin of Ki-4 scFv. As discussed above, Ki-4 is a Cluster A antibody. Cluster A antibodies have been shown not to be cytostatic or cytotoxic to a Hodgkin's disease cell in the absence of a cytostatic or cytotoxic agent. The combination of Lemke and Barth fails to teach or suggest an antibody that is cytostatic or cytotoxic to a Hodgkin's disease cell line in the absence of a cytostatic or cytotoxic agent as claimed in claim 6. Thus, the combination of Lemke and Barth cannot render claim 6 obvious.

Claims 14, 17 and 18 each depend from claims 8 and 11. Claim 8 requires that the recited protein compete for binding to CD30 with antibodies AC10 or HeFi-1. As discussed above, Lemke does not teach or suggest for therapeutic use a protein which competes for binding to CD30 antibodies with AC10 or HeFi-1. The immunotoxin disclosed in Barth is based on antibody Ki-4, which does not compete with AC10 or HeFi-1 (*see* Lemke, Table II). Thus, Barth does not satisfy the deficiency of Lemke in that it does not teach a protein that competes with AC10 or HeFi-1. Thus, the combination of Lemke and Barth fails to teach this limitation of claim 8. Claim 11 specifies that the recited protein comprise an amino acid sequence that has at least 95% sequence identity to SEQ ID NO: 2 (the sequence of the heavy chain variable region of AC10). As discussed above, Lemke fails to teach for therapeutic use a protein comprising such an amino acid sequence. Barth fails to supply this missing teaching because it discloses for therapeutic use only a derivative of an antibody, Ki-4, that is taught by Lemke. Thus, the combination of Lemke and Barth fails to teach every limitation of claims 8 and 11, and the combination therefore cannot render obvious claims 14, 17 and 18.

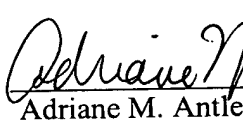
For the above reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 6, 14, 17 and 18 as obvious under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully request consideration of the foregoing remarks and entry of the foregoing amendments into the file of the above-identified application. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Date: October 2, 2003



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Adriane M. Antler (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090